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Polyunsaturated fatty acids and suicide risk in mood disorders: A systematic review

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ABSTRACT

Deficiency of omega-3 polyunsaturated fatty acids (PUFAs) and an alteration between the ratio of omega-3 and omega-6 PUFAs may contribute to the pathogenesis of bipolar disorder and unipolar depression. Recent epidemiological studies have also demonstrated an association between the depletion of PUFAs and suicide. Our aim was to investigate the relationship between PUFAs and suicide; assess whether the depletion of PUFAs may be considered a risk factor for suicidal behavior; in addition to detailing the potential use of PUFAs in clinical practice. We performed a systematic review on PUFAs and suicide in mood disorders, searching MedLine, Excerpta Medica, PsycLit, PsycInfo, and Index Medicus for relevant epidemiological, post-mortem, and clinical studies from January 1997 to September 2016. A total of 20 articles from peer-reviewed journals were identified and selected for this review. The reviewed studies suggest that subjects with psychiatric conditions have a depletion of omega-3 PUFAs compared to control groups. This fatty acid depletion has also been found to contribute to suicidal thoughts and behavior in some cases. However, large epidemiological studies have generally not supported this finding, as the depletion of omega-3 PUFAs was not statistically different between controls and patients diagnosed with a mental illness and/or who engaged in suicidal behavior. Increasing PUFA intake may be relevant in the treatment of depression, however in respect to the prevention of suicide, the data is currently not supportive of this approach. Changes in levels of PUFAs may however be a risk factor to evaluate when assessing for suicide risk. Clinical studies should be conducted to prospectively assess whether prescriptive long-term use of PUFAs in PUFA-deficient people with depression, may have a preventative role in attenuating suicide.

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1. Introduction

Omega-3 (n-3) and omega-6 (n-6) fatty acids are in the group of polyunsaturated fatty acids (PUFAs) because their chain consists of several double bonds. The human body synthesizes omega–3 fatty acids from α-linolenic acid (De Gomez and Brenner, 1975) and this is possible through the competitive presence of omega–6 fatty acids, which are crucial chemical analogues derived by linoleic acid (De Gomez and Brenner, 1975; Hangue and Christofferson, 1984). Food is the essential source of both the omega − 3 α-linolenic acid and omega − 6 linoleic acid as short chain fatty acids may be not converted into long chain fatty acids by humans; therefore the tissue composition of n-3 PUFAs are crucially related to dietary consumption (Arterburn et al., 2006). Moreover n-3 and n-6 serum levels can be influenced by single nucleotide polymorphisms (SNPs) in fatty acid desaturase (FADS) genes, which are partially involved in metabolic inter-conversion (Kiecolt-Glaser et al., 2010). Certain SNPs are potential modifying factors of the pharmacological treatment of psychiatric conditions (Evans et al., 2012), however it is relatively unknown as to which SNPs may be implicated in modifying the pharmacokinetics and pharmacodynamics of PUFAs.

Omega-6 fatty acids may be considered a family of polyunsaturated fatty acids, having vegetable origin as well as the first carbon–carbon double bond in the n-6 position. The most important fatty acids within the omega-6 group are represented by: linoleic acid (18: 2), an essential fatty acid, and the arachidonic acid (20: 4), which is a precursor of prostaglandins (see Fig. 1). The competitive relationship with omega 3 fatty acids seems to modulate the potential pro-inflammatory effect of the omega-6 fatty acids. However, the most studied PUFAs are the omega-3 fatty acids. The omega-3 fatty acids share a carbon–carbon double bond in the n-3 position. The most important fatty acids within the omega-3 group are listed as follows: α-linolenic acid or ω3α (18: 3; ALA), eicosapentaenoic acid (20: 5, EPA), and docosahexaenoic acid (22: 6, DHA) (see Fig. 1).

Various chronic psychiatric diseases report an imbalance in terms of omega 6/omega 3 ratio (Simopoulos, 2008). The omega-3 oils are involved in transmitting signals, moods and emotions (Lakhan and Viera, 2008); and levels are very low for instance in most bipolar patients (Osher et al., 2005). Research suggests that omega-3 fatty acid depletion can be involved in the pathogenesis of both bipolar disorder (BD) and major depressive disorder (MDD) (Freeman et al., 2006; Hibbeln, 1998; Noaghiul and Hibbeln, 2003; Peet, 2004). Patients with MDD have shown a significant decrease in red blood cell (RBC) membrane DHA composition (Edwards et al., 1998; Peet et al., 1998) together with specific deficits in DHA composition of the orbitofrontal cortex according to post-mortem studies (McNamara et al., 2007a). Significant reductions have also been reported in RBC DHA and arachidonic acid composition among patients with BD (Chiu et al., 2003); however, the fatty acid composition of post-mortem brain tissue is poorly understood.

High fish consumption is associated with a reduced occurrence of psychiatric disorders (such as MDD and BD) and of psychopathological symptoms (impulsivity and aggression), and this decreased occurrence has in part been associated with omega-3 fatty acid levels (Bozzatello et al., 2016; Hibbeln, 2009; Reis and Hibbeln, 2006). The current knowledge on DHA/EPA for brain function does not generate a rational daily intake recommendation, therefore the existing recommendations for cardiovascular protection could be taken as a minimum for brain protection (Parris, 2007). The American Heart Association recommends a minimum intake of two fish meals weekly for primary cardiovascular protection and 1000 mg/day of DHA/EPA for protection against a second heart attack (Parris, 2007). In Europe, different studies (one Norwegian and one German) recommend taking approximately one or two grams of DHA/EPA in healthy subjects (Eritsland, 2000; Von Schacky, 2006).

In patients with psychiatric disorders, it has been demonstrated that a dose of up to 9.6 g is commonly safe and effective (Stoll et al., 1999), furthermore Hibbeln suggested that pregnant women may consider consuming a minimum 650 mg/day of DHA and EPA (with a minimum 300 mg/day of DHA) to prevent postpartum depression (Hibbeln, 1998).

In mice, Tang et al. found that not only total dietary fat content but the forms of omega-3 fatty acids contributed to the effects of omega-3 fatty acids. DHA-PL (DHA and phospholipid) could increase DHA concentration in the liver and brain during a short period and the increase of DHA level is much more significant in the liver than in the brain (Tang et al., 2012). The efficiency of PL (phospholipid) bound omega-3s is more significant than EE (ethyl ester) or FFA (free fatty acids) forms in increasing DHA concentration in tissues. This result was probably due to the difference in absorption and distribution of different omega-3 formulation (Tang et al., 2012). Other studies have shown that long-term DHA intake could particularly increase cerebral DHA level (Suzuki et al., 1988; Hashimoto et al., 2005; Shirai et al., 2006; Gamoh et al., 1999).

1.1. Etiological hypotheses

PUFAs play central roles in different physiological functions (Lands, 2007; Lewis et al., 2011). Mechanisms that may underlie the association between omega-3 fatty acid insufficiency and the emergence of psychiatric disorders include several factors: a reduction of serotonin and dopamine levels (De la Presa and Innis, 1999; Levant, 2013; Schneider et al., 2016), an impaired neuronal migration and altered connectivity, timed apoptosis together with abnormalities in the dendritic arborization such that related to an irreversible disruption in those neuronal pathways involved in the regulation of behaviors (Sinclair et al., 2007; Hibbeln et al., 2004; Lakhan and Viera, 2008), neuroinflammatory processes (Farooqui et al., 2007; McGorry et al., 2014; Levant, 2013; Schneider et al., 2016), and hypothalamic pituitary adrenal axis dysregulation (Hibbeln et al., 2004; Levant, 2013; Schneider et al., 2016).